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     (FILE 'HOME' ENTERED AT 18:11:26 ON 29 AUG 2000)

     INDEX 'ADISALERTS, ADISINSIGHT, AGRICOLA, AIDSLINE, ANABSTR, AQUASCI,
     BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO,
CABA,
     CANCERLIT, CAPLUS, CEABA, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU,
     DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 18:11:35 ON 29 AUG
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               SEA JNK3 OR SAPK
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                3   FILE ADISALERTS
                3   FILE ADISINSIGHT
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                1   FILE BIOBUSINESS
                1   FILE BIOCOMMERCE
              675   FILE BIOSIS
                7   FILE BIOTECHABS
                7   FILE BIOTECHDS
              396   FILE BIOTECHNO
                9   FILE CABA
              375   FILE CANCERLIT
              655   FILE CAPLUS
                1   FILE CIN
                7   FILE CONFSCI
               42   FILE DDFU
              243   FILE DGENE
                2   FILE DRUGNL
               56   FILE DRUGU
               22   FILE EMBAL
              536   FILE EMBASE
              530   FILE ESBIOBASE
                1   FILE FSTA
               44   FILE GENBANK
                2   FILE IFIPAT
               28   FILE JICST-EPLUS
                1   FILE KOSMET
              313   FILE LIFESCI
              608   FILE MEDLINE
                1   FILE NIOSHTIC
                7   FILE NTIS
                2   FILE PHIN
               11   FILE PROMT
              696   FILE SCISEARCH
              128   FILE TOXLINE
              161   FILE TOXLIT
               34   FILE USPATFULL
               22   FILE WPIDS
               22   FILE WPINDEX
L1              QUE JNK3 OR SAPK
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     FILE 'MEDLINE, EMBASE, CANCERLIT, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT
     18:12:58 ON 29 AUG 2000
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| L2 | 3481 | S L1 AND (EXPRES? OR ACTIVA?) |
| L3 | 308 | S L2 AN[redacted]ODULA? |
| L4 | 198 | S L3 AND INHIBI? |
| L5 | 53 | DUP REM L4 (145 DUPLICATES REMOVED) |
| L6 | 2 | S L5 AND ANTISENSE |
| L7 | 7 | S L5 AND ANTIBODY |

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L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:10570 CAPLUS
DOCUMENT NUMBER: 132:73665
TITLE: **Antisense modulation** of Jun N-terminal kinase kinase-1 **expression**
INVENTOR(S): Ward, Donna T.; Cowsert, Lex M.
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., USA
SOURCE: U.S., 32 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6010906 | A | 20000104 | US 1999-358382 | 19990721 |

AB **Antisense** compds., compns. and methods are provided for **modulating** the **expression** of Jun N-terminal kinase kinase-1 (JNKK1, also known as PRKMK4, MEK4, MKK4, **SAPK**/ERK kinase 1, and SEK1). The compns. comprise **antisense** compds., particularly **antisense** oligonucleotides, targeted to nucleic acids encoding Jun N-terminal Kinase Kinase-1. Methods of using these compds. for **modulation** of Jun N-terminal Kinase Kinase-1 **expression** and for treatment of diseases assocd. with **expression** of Jun N-terminal Kinase Kinase-1 are provided. Twenty-three uniformly phosphorothioated oligonucleotides **inhibited** the **expression** of JNKK1 by .gtoreq.20%, and 31 chimeric phosphorothioated oligonucleotides with 2'-methoxyethyl gapmer structures demonstrated .gtoreq.30% **inhibition** of JNKK1 **expression**.

REFERENCE COUNT: 18
REFERENCE(S):
(1) Anon; WO 9854203 1998 CAPLUS
(2) Butterfield; Biochem J 1999, V338, P681 CAPLUS
(3) Cuenda; Biochem J 1998, V333, P11 CAPLUS
(4) Davis; US 5736381 1998 CAPLUS
(7) Derijard; Science 1995, V267, P682 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:141274 CAPLUS
DOCUMENT NUMBER: 130:218272
TITLE: **Antisense** oligonucleotide compositions and methods for the **modulation** of JNK proteins
INVENTOR(S): Mckay, Robert; Dean, Nicholas; Monia, Brett P.; Nero, Pamela Scott; Gaarde, William A.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 190 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

WO 9909214 A1 19990225 WO 1998-US16488 19980807
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 5877309 A 19990302 US 1997-910629 19970813
AU 9887750 A1 19990308 AU 1998-87750 19980807
EP 1003916 A1 20000531 EP 1998-939287 19980807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRIORITY APPLN. INFO.: US 1997-910629 19970813
WO 1998-US16488 19980807

AB Compns. and methods for the treatment and diagnosis of diseases or disorders amenable to treatment through **modulation** of **expression** of a gene encoding a Jun N-terminal kinase (JNK protein) are provided. Oligonucleotide are herein provided which are specifically hybridizable with nucleic acids encoding JNK1, JNK2 and **JNK3**, as well as other JNK proteins and specific isoforms thereof. Methods of treating animals suffering from diseases or disorders amenable to therapeutic intervention by **modulating** the **expression** of one or more JNK proteins with such oligonucleotide are also provided. Methods for the treatment and diagnosis of diseases or disorders assocd. with aberrant **expression** of one or more JNK proteins are also provided. The invention is thus directed to compns. for **modulating**, diagnostic methods for detecting, and therapeutic methods for **inhibiting**, the hyperproliferation of cells and formation, development and maintenance of tumors.

REFERENCE COUNT: 3
REFERENCE(S):
(1) Derijard, B; Cell 1994, V76, P1025 CAPLUS
(2) Gupta, S; The EMBO Journal 1996, V15(11), P2760 CAPLUS
(3) Seimiya, H; J Biological Chemistry 1997, V272, P4631 CAPLUS

=> d L7 ibib ab 1-7

L7 ANSWER 1 OF 7 MEDLINE
ACCESSION NUMBER: 2000148852 MEDLINE
DOCUMENT NUMBER: 20148852
TITLE: Brain-derived neurotrophic factor-induced phosphorylation of neurofilament-H subunit in primary cultures of embryo rat cortical neurons.
AUTHOR: Tokuoka H; Saito T; Yorifuji H; Wei F; Kishimoto T; Hisanaga S
CORPORATE SOURCE: Laboratory of Cell and Developmental Biology, Faculty of Biosciences, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226-8501, Japan.. hisanaga-shinichi@c.metro-u.ac.jp
SOURCE: JOURNAL OF CELL SCIENCE, (2000 Mar) 113 ( Pt 6) 1059-68. Journal code: HNK. ISSN: 0021-9533.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY WEEK: 20000801

AB Phosphorylation of the neurofilament-H subunit (NF-H) was investigated in rat embryonic brain neurons in culture. A portion of the NF-H was phosphorylated in vivo at embryonic day 17 when brain neurons were prepared. When the neurons were isolated and cultured, the NF proteins

disappeared once and then reappeared over the next several days in the following order: (1) NF-L/NF-M, (2) dephosphorylated NF-H and (3) phosphorylated NF-H. Phosphorylation of NF-H began around 4 days after cell plating, at about the time of synapse formation. Treatments that appeared to **modulate** the timing of synapse formation also affected the timing of NF-H phosphorylation: (1) earlier phosphorylation was observed at higher neuronal cell density, (2) earlier phosphorylation was observed in neurons cultured on a coating substrate that promotes rapid neurite extension and (3) phosphorylation was suppressed when neurite extension was **inhibited** by brefeldin A. Three possible synapse formation-induced events, excitation, cell-cell contact through adhesion proteins and elevated concentrations of neurotrophic factors, were examined for their possible involvement in generating the signal for NF-H phosphorylation. Neither excitation nor cell contact enhanced NF-H phosphorylation. Neurotrophic factors, brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT3) stimulated phosphorylation of NF-H. The BDNF-stimulated phosphorylation was **inhibited** by an anti-BDNF **antibody** and K252a, an **inhibitor** of BDNF receptor TrkB tyrosine kinase. Among known NF-H kinases of cyclin-dependent kinase 5 (CDK5), external signal-regulated protein kinase (ERK) and stress-**activated** protein kinase (**SAPK**), CDK5 and **SAPK** showed an increase in kinase activity or an active form with a time course similar to NF-H phosphorylation in control culture. On the other hand, BDNF stimulated the kinase activity of CDK5 and induced appearance of an active form of ERK transiently. These results suggest a possibility that synapse formation induces NF-H phosphorylation, at least in part, through **activation** of CDK5 by BDNF.

L7 ANSWER 2 OF 7 MEDLINE
ACCESSION NUMBER: 2000088659 MEDLINE
DOCUMENT NUMBER: 20088659
TITLE: **Modulation** of tau phosphorylation and intracellular localization by cellular stress.
AUTHOR: Jenkins S M; Zinnerman M; Garner C; Johnson G V
CORPORATE SOURCE: Department of Psychiatry, University of Alabama at Birmingham, 1720 7th Avenue South, Sparks Center, Birmingham, AL 35924, USA.
CONTRACT NUMBER: AG06569 (NIA)
AG12978 (NIA)
SOURCE: BIOCHEMICAL JOURNAL, (2000 Jan 15) 345 Pt 2 263-70.
Journal code: 9YO. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200005
ENTRY WEEK: 20000501

AB Tau is a microtubule-associated protein that is functionally **modulated** by phosphorylation and hyperphosphorylated in several neurodegenerative diseases. Because phosphorylation regulates both normal and pathological tau functioning, it is of great interest to identify the signalling pathways and enzymes capable of **modulating** tau phosphorylation in vivo. The present study examined changes in tau phosphorylation and localization in response to osmotic stress, which **activates** the stress-**activated** protein kinases (**SAPKs**), a family of proline-directed protein kinases shown to phosphorylate tau in vitro and hypothesized to phosphorylate tau in Alzheimer's disease. Immunoblot analysis with phosphorylation-dependent **antibodies** revealed that osmotic stress increased tau phosphorylation at the non-Ser/Thr-Pro sites Ser-262/356, within the microtubule-binding domain, as well as Ser/Thr-Pro sites outside of tau's microtubule-binding domain. Although all **SAPKs** examined were **activated** by osmotic stress, none of the endogenous **SAPKs** mediated the increase in tau phosphorylation. However, when transfected into SH-SY5Y cells, SAPK3, but not the other **SAPKs** examined,

phosphorylated tau in situ in response to **activation** by osmotic stress. Osmotic-stress-induced tau phosphorylation correlated with a decrease in the amount of tau associated with the cytoskeleton and an increase in the amount of soluble tau. This stress-induced alteration in tau localization was only partially due to phosphorylation at Ser-262/356 by a staurosporine-sensitive, non-proline-directed, protein kinase. Taken together, these results suggest that osmotic stress **activates** at least two tau-directed protein kinases, one proline-directed and one non-proline-directed, that SAPK3 can phosphorylate tau on Ser/Thr-Pro residues in situ, and that Ser-262/356 phosphorylation only partially regulates tau localization in the cell.

L7 ANSWER 3 OF 7 MEDLINE
ACCESSION NUMBER: 1999384858 MEDLINE
DOCUMENT NUMBER: 99384858
TITLE: Mechanical endothelial damage results in basic fibroblast growth factor-mediated **activation** of extracellular signal-regulated kinases.
AUTHOR: Pintucci G; Steinberg B M; Seghezzi G; Yun J; Apazidis A; Baumann F G; Grossi E A; Colvin S B; Mignatti P; Galloway A C
CORPORATE SOURCE: Department of Surgery, New York University School of Medicine, New York, USA.
SOURCE: SURGERY, (1999 Aug) 126 (2) 422-7. Journal code: VC3. ISSN: 0039-6060.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199911
AB BACKGROUND: Endothelial damage, such as that associated with balloon angioplasty or preparation of veins for bypass grafts, results in intimal hyperplasia. Growth factors and cytokines that **modulate** endothelial cell functions through various intracellular signaling pathways mediate rapid endothelial repair, which may prevent or reduce restenosis. Here we investigated the effect of mechanical injury of endothelial cells on the mitogen-**activated** kinase signaling pathways, extracellular-signal-regulated kinases (ERKs), C-Jun N-terminal kinase (JNK/**SAPK**), and p38. METHODS: Confluent human umbilical vein endothelial cells or bovine aortic endothelial cells were wounded with a razor blade; mitogen-**activated** kinase **activation** was monitored by immunoblotting with **antibodies** to active ERK, JNK/**SAPK**, or p38. RESULTS: Wounding of human umbilical vein endothelial cell or bovine aortic endothelial cell monolayers resulted in rapid (5-minute) **activation** of ERK-1 and -2, which was abolished by monoclonal **antibody** to basic fibroblast growth factor (FGF-2). This **antibody** or an **inhibitor** of ERK **activation**, PD98059, also blocked endothelial cell migration after the wounding. Thus FGF-2-induced ERK **activation** mediates the endothelial response to wounding. CONCLUSIONS: ERK-1 and -2 are **activated** by FGF-2 released from endothelial cells in response to injury. Therapeutic strategies aimed at reducing FGF-2-induced intimal hyperplasia should preserve ERK **activation** in endothelial cells while abolishing it in smooth muscle cells.

L7 ANSWER 4 OF 7 MEDLINE
ACCESSION NUMBER: 1999021719 MEDLINE
DOCUMENT NUMBER: 99021719
TITLE: Evidence for involvement of mitogen-**activated** protein kinase, rather than stress-**activated** protein kinase, in potentiation of 1-beta-D-arabinofuranosylcytosine-induced apoptosis by interruption of protein kinase C signaling.
AUTHOR: Jarvis W D; Fornari F A Jr; Tombes R M; Erukulla R K;

Bittman R; Schwartz G K; Dent P; Grant S
CORPORATE SOURCE: Department of Medicine, Medical College of Virginia, Richmond, Virginia 23298, USA.
CONTRACT NUMBER: CA63753 (NCI)
CA77141 (NCI)
HL16660 (NHLBI)
+
SOURCE: MOLECULAR PHARMACOLOGY, (1998 Nov) 54 (5) 844-56.
Journal code: NGR. ISSN: 0026-895X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199902
ENTRY WEEK: 19990204

AB The stress-**activated** protein kinase (**SAPK**) and mitogen-**activated** protein kinase (MAPK) cascades mediate cytotoxic and cytoprotective functions, respectively, in the regulation of leukemic cell survival. Involvement of these signaling systems in the cytotoxicity of 1-beta-D-arabinofuranosylcytosine (ara-C) and **modulation** of ara-C lethality by protein kinase C PKC **inhibition**/down-regulation was examined in HL-60 promyelocytic leukemia cells. Exposure to ara-C (10 microM) for 6 hr promoted extensive apoptotic DNA damage and cell death, as well as **activation** of PKC. This response was accompanied by downstream **activation** of the **SAPK** and MAPK cascades. PKC-dependent MAPK activity seemed to limit ara-C action in that the toxicity of ara-C was enhanced by pharmacological reductions of PKC, MAPK, or both. Thus, ara-C action was (1) partially attenuated by diradylglycerols, which stimulated PKC and MAPK, but (2) dramatically amplified by sphingoid bases, which **inhibited** PKC and MAPK. The cytotoxicity of ara-C also was substantially increased by pharmacological reductions of PKC, including down-regulation of PKC by chronic preexposure to the macrocyclic lactone bryostatin 1 or **inhibition** of PKC by acute coexposure to the dihydrosphingosine analog safingol. Significantly, both of these manipulations prevented **activation** of MAPK by ara-C. Moreover, acute disruption of the MAPK module by AMF, a selective **inhibitor** of MEK1, suppressed both basal and drug-stimulated MAPK activity and sharply increased the cytotoxicity of ara-C, suggesting the direct involvement of MAPK as a downstream antiapoptotic effector for PKC. None of these chemopotentiating agents enhanced ara-CTP formation. Ceramide-driven **SAPK** activity did not seem to mediate drug-induced apoptosis, given that (1) neutralization of endogenous tumor necrosis factor-alpha with monoclonal **antibodies** or soluble tumor necrosis factor receptor substantially reduced ceramide generation and **SAPK activation** by ara-C, whereas the induction of apoptosis was unaffected; (2) pharmacological **inhibition** of sphingomyelinase by 3-O-methoxysphingomyelin reduced ceramide generation and **SAPK activation** without limiting the drug's cytotoxicity; and (3) potentiation of ara-C action by bryostatin 1 or safingol was not associated with further stimulation of **SAPK**. These observations collectively suggest a primary role for decreased MAPK, rather than increased **SAPK**, in the potentiation of ara-C cytotoxicity by interference with PKC-dependent signaling.

L7 ANSWER 5 OF 7 MEDLINE
ACCESSION NUMBER: 1998429485 MEDLINE
DOCUMENT NUMBER: 98429485
TITLE: Stress-**activated** protein kinases are negatively regulated by cell density.
AUTHOR: Lallemand D; Ham J; Garbay S; Bakiri L; Traincard F; Jeannequin O; Pfarr C M; Yaniv M
CORPORATE SOURCE: Unite des Virus Oncog`enes, Unite associee 1644 du Centre National de la Recherche Scientifique, Paris Cedex 15

France.
SOURCE: EMB[redacted]OURNAL, (1998 Oct 1) 17 (19) 5[redacted]-26.
Journal code: EMB. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
AB Stimulation by UV irradiation, TNFalpha, as well as PDGF or EGF **activates** the JNK/**SAPK** signalling pathway in mouse fibroblasts. This results in the phosphorylation of the N-terminal domain of c-Jun, increasing its transactivation potency. Using an **antibody** that specifically recognizes c-Jun phosphorylated at Ser63, we show that culture confluency drastically **inhibited** c-Jun N-terminal phosphorylation due to the **inhibition** of the JNK/**SAPK** pathway. Transfection experiments demonstrate that the **inhibition** occurs at the same level as, or upstream of, the small G-proteins cdc42 and Rac1. In contrast, the classical MAPK pathway was insensitive to confluency. The **inhibition** of JNK/**SAPK** **activation** depended on the integrity of the actin microfilament network. These results were confirmed and extended in monolayer wounding experiments. After PDGF, EGF or UV stimulation, c-Jun was predominantly phosphorylated in cells bordering the wound, which are the cells that move to occupy the wounded area. Thus, **modulation** of the stress-dependent signal cascade by confluency will restrict c-Jun N-terminal phosphorylation in response to mitogenic or chemotactic agents to cells that border a wounded area.

L7 ANSWER 6 OF 7 MEDLINE
ACCESSION NUMBER: 97132937 MEDLINE
DOCUMENT NUMBER: 97132937
TITLE: Interleukin-6 **inhibits** Fas-induced apoptosis and stress-**activated** protein kinase **activation** in multiple myeloma cells.
AUTHOR: Chauhan D; Kharbanda S; Ogata A; Urashima M; Teoh G; Robertson M; Kufe D W; Anderson K C
CORPORATE SOURCE: Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, MA 02115, USA.
CONTRACT NUMBER: CA 50947 (NCI)
SOURCE: BLOOD, (1997 Jan 1) 89 (1) 227-34.
Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199704
AB Fas belongs to the family of type-1 membrane proteins that transduce apoptotic signals. In the present studies, we characterized signaling during Fas-induced apoptosis in RPMI-8226 and IM-9 multiple myeloma (MM) derived cell lines as well as patient plasma cell leukemia cells. Treatment with anti-Fas (7C11) monoclonal **antibody** (MoAb) induced apoptosis, evidenced by internucleosomal DNA fragmentation and propidium iodide staining, and was associated with increased **expression** of c-jun early response gene. We also show that anti-Fas MoAb treatment is associated with **activation** of stress-**activated** protein kinase (**SAPK**) and p38 mitogen-**activated** protein kinase (MAPK); however, no detectable increase in extracellular signal-regulated kinases (ERK1 and ERK2) activity was observed. Because interleukin-6 (IL-6) is a growth factor for MM cells and **inhibits** apoptosis induced by dexamethasone and serum starvation, we examined whether IL-6 affects anti-Fas MoAb-induced apoptosis and **activation** of **SAPK** or p38 MAPK in MM cells. Culture of MM cells with IL-6 before treatment with anti-Fas MoAb significantly

reduced both DNA fragmentation and **activation** of **SAPK**, without altering inhibition of p38 MAPK activity. The results therefore suggest that anti-Fas MoAb-induced apoptosis in MM cells is associated with **activation** of **SAPK**, and that IL-6 may both **inhibit** apoptosis and **modulate SAPK** activity.

L7 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:819406 CAPLUS
DOCUMENT NUMBER: 132:60991
TITLE: Mitogen and stress-**activated** protein kinase-1 and MSK2 and their regulation and encoding polynucleotides
INVENTOR(S): Alessi, Dario; Deak, Maria; Cohen, Philip; Caivano, Matilde
PATENT ASSIGNEE(S): Medical Research Council, UK
SOURCE: PCT Int. Appl., 167 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9967283 | A2 | 19991229 | WO 1999-GB1660 | 19990608 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9942730 | A1 | 20000110 | AU 1999-42730 | 19990608 |
| PRIORITY APPLN. INFO.: | | | GB 1998-13467 | 19980624 |
| | | | GB 1998-17303 | 19980810 |
| | | | WO 1999-GB1660 | 19990608 |

AB Substantially pure two-kinase-domain protein kinases are provided and designated mitogen and stress-**activated** protein kinases-1 and -2 (MSK1 and MSK2). Their cDNA and deduced amino acid sequences are provided. MKS1 and MKS2 are **activated** in vitro and vivo by either the MAPK/ERK or SAPK2/p38 cascade systems, and appear to mediate the **activation** of transcription factors CREB and ATF1 by growth factors and stress signals. MSK1 is localized in the nucleus of cells and phosphorylates CREB at serine-133; a synthetic peptide corresponding to the sequence surrounding serine-133 is phosphorylated with a remarkably low Km value (<0.1 .mu.M). The effects of SB203580 and PD98059 on the EGF, UV, and TNF-induced **activation** of CREB and ATF1 mirror the effects of these **inhibitors** on MSK1 **activation**. MSK1 and MSK2 may regulate the transcription of the genes for proinflammatory mediators cyclooxygenase-2 (COX2) and interleukin-1 and the induction of the proinflammatory COX2 protein. Variants, fusions, fragments, or derivs. thereof useful in screening assays for drugs are also provided, as are applications of the kinases in the **modulation** of CREB and COX2 activities..